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BCAA was more closely associated with visceral fat area than subcutaneous fat area in patients of type 2 diabetes mellitus: a cross-sectional study

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Abstract

Background Branched-chain amino acid (BCAA) has been reported to be associated with obesity, the association of BCAA with visceral fat area (VFA) and subcutaneous fat area (SFA) remained unclear in patients with type 2 diabetes.

Methods This cross-sectional study was conducted in 284 patients with type 2 diabetes mellitus. Enzyme-linked immunospecific assay was used to measure levels of serum BCAA and branched-chain keto acid (BCKA). VFA and SFA were measured with bio-impedance analysis method. The association between BCAA and VFA was calculated using Pearson correlation and multivariable linear regression analysis.

Results There were significant differences in the means of body mass index, waist circumstance, SFA and VFA among the three groups divided by total BCAA tertiles (all $p < 0.05$). Compared to patients with lower levels of serum BCAA (the lower tertile group), the means of VFA and SFA were significantly larger in the middle and upper tertile groups (all $p < 0.05$). However, the differences in above obesity parameters were nonsignificant according to various BCKA tertiles. Pearson correlation analysis also demonstrated that BCAA levels were positive associated with each obesity parameter ($p < 0.05$). Nevertheless, multivariable linear regression analysis showed that levels of serum BCAA were correlated with VFA, BMI and WC (all $p < 0.05$) rather than SFA after adjusted for other confounders.

Conclusions levels of serum BCAA were more closely correlated with VFA than SFA, prospective studies should be warranted to further explore the mechanism mediating BCAA and visceral fat accumulation in Human beings.

Clinical trial number Not applicable.

Keywords Branched-chain amino acids, Visceral fat area, Subcutaneous fat area, Obesity, Type 2 diabetes

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Background

Globally, 39% of adults were overweight and 13% were obese according to the World Health Organization report released 2021 [1]. Obesity is associated with the development or aggravation of cardiometabolic diseases, such as insulin resistance, dyslipidemia, hypertension cardiovascular disease and particularly type 2 diabetes [2]. Obesity-related comorbidities caused serious socioeconomic burden worldwide [3]. Poor lifestyle habits, including smoking, excessive alcohol consumption, physical inactivity and unbalanced diets, have been established to account for the booming of obesity and obesity-associated diseases [4]. In the past, it was believed that obesity resulted from high-fat and high-calorie diet [5]. Recently, researchers found that excessive intake or malmetabolism of branched-chain amino acid (BCAA) was also associated with many morbidities including obesity, insulin resistance, dyslipidemia, diabetes and even pancreatic cancer [6–8].

A majority of studies demonstrated that BCAA intake as well serum BCAA levels were positively associated with general and abdominal obesity [8–10], while restriction of BCAA intake in diet has been reported to ameliorate obesity in Humans and rodents [11]. However, there were some concerns. Firstly, the association between BCAA and obesity was controversial as an inverse association between dietary BCAA and prevalence of obesity has also been reported [12, 13]. Secondly, previous studies focused on obesity indices such body mass index (BMI) and waist circumstance (WC) [8, 10], a few studies explored the relationship between BCAA and visceral fat area (VFA), an obesity parameter closely associated with insulin resistance and onset of diabetes [14, 15]. Furthermore, previous studies mainly concentrated on obese adolescents, middle-aged and elderly population, or patients with polycystic ovary syndrome [8, 16, 17], the association between BCAA and obesity was seldomly studied in patients with type 2 diabetes, though elevated levels of serum BCAA has been reported in these individuals [18].

Therefore, we explored the relationship of circulating BCAA and its primary metabolite branched-chain keto acid (BCKA) with subcutaneous fat area (SFA) and VFA in patients with type 2 diabetes.

Methods

Study design and patients

Patients were recruited from the Department of Endocrinology, Putuo Hospital, Shanghai University of Traditional Chinese Medicine from January 1st, 2021 to August 30th, 2023. Type 2 diabetes was defined in accordance with the criteria of The American Diabetes Association [19]. We excluded patients as following: severe hepatic or renal insufficiency; type 1 diabetes mellitus or gestational diabetes; malignant tumors; severe infections or traumatic diseases; cognitive dysfunction or psychiatric disorders. Finally, 284 patients (105 females and 179 males) with type 2 diabetes mellitus were enrolled in this cross-sectional study.

The study was approved by the Ethics Committee of Department of Endocrinology, Putuo Hospital, Shanghai University of Traditional Chinese Medicine with the Declaration of Helsinki (Number of approval form of ethics committee: PTEC-A-2024-40(S)-1). Informed consents were acquired from all subjects.

Anthropometric and biochemical measurements

Anthropometric measurements including height, weight, WC and hip circumferences (HC) were measured by a trained nurse. Body mass index (BMI, kg/m^2) was calculated as dividing the weight by height squared. VFA and SFA was determined using bioimpedance analysis method (OMRON, Tokyo).

Venous blood samples were drawn after an overnight fast of at least 10 h. Biochemical Indexes including fasting blood glucose, fasting insulin, postprandial blood glucose, triglycerides, total cholesterol, high- density lipoprotein - cholesterol (HDL-C), and low- density lipoprotein -cholesterol (LDL-C) were assayed by Roche cobas 8000 fully automated biochemical analyzer. Enzyme-linked immunospecific assay was used to measure serum BCAA (abcam, ab83374, USA) and BCKA (Fu sheng Biologicals, A137748, Shanghai, China). Participants were classified into three groups according to total BCAA levels (including leucine, isoleucine and valine): lower tertile ≤ 2.20 mmol/L (n = 94), 2.20 mmol/L < middle tertile < 2.88 mmol/L (n = 95), upper tertile ≥ 2.88 mmol/L (n = 95). Patients were also divided into three groups based on BCKA levels: lower tertile ≤ 121.4 umol/L (n = 94), 121.4 umol/L < middle tertile < 130.6 umol/L (n = 95), upper tertile ≥ 130.6 umol/L (n = 95).

Statistical analysis

Continuous variables were expressed as median (interquartile range), and categorical variables as number (percentage). Kruskal–Wallis test examined differences in medians among three groups (Table 1, supplementary Table 1). Differences in proportions were tested using the chi-square test. The general linear model was utilized to compare obesity indices according to tertiles of serum BCKA and BCAA, and LSD method was applied for post-hoc between-group comparison (Fig. 1). Pearson correlation analysis was used to evaluate the association of BCAA with obesity parameters (Fig. 2). Multiple linear regression analysis was used to examine the association of BCAA and BCKA with obesity parameters considering other clinical parameters (Table 2). All the analyses were performed using SPSS 26.0 (IBM SPSS Statistics

Table 1 Characteristics of study participants with different serum BCAA levels

Variables	BCAAs tertiles			*P* value
	Lower tertile (*n* = 94)	Middle tertile (*n* = 95)	Upper tertile (*n* = 95)	
Gender, male	55 (58.5)	55 (57.9)	69 (72.4)	0.044
Age, years	63.0 (55.8–67.3)	63.0 (58.0–69.0)	60.0 (48.0–66.0)	0.040
Duration of diabetes, years	7.0 (0.2–17.5)	7.0 (1.0–20.0)	6.0 (0.2–16.0)	0.65
Current smoker, %	18 (19.1)	22 (23.2)	15 (15.8)	0.56
Current drinkers, %	12 (12.8)	12 (12.6)	15 (15.8)	0.54
BMI, kg/m^2	24.2 (21.5–26.0)	25.0 (23.0–27.2)	25.3 (23.5–28.0)	0.003
WC, cm	90.0 (84.0–95.1)	93.0 (87.0–98.9)	92.6 (88.8–101)	0.001
HTN, %	65 (69.4)	69 (72.6)	62 (65.3)	0.56
SBP, mmHg	133 (125–147)	130 (123–144)	136 (127–147)	0.42
DBP, mmHg	81 (79–90)	80 (75–89)	82 (78–89)	0.38
FPG, mmol/L	7.37 (5.70–10.0)	8.00 (6.10–10.5)	7.90 (6.20–10.6)	0.30
HbA1c, %	9.9 (8.3–12.3)	9.5 (7.9–11.5)	9.2 (7.6–10.9)	0.17
F-INS, pmol/L	61.9 (34.6–110)	74.9 (43.3–125)	67.7 (41.1–103)	0.48
HOMA-IR, mmol/L*mU/L	3.11 (1.52–5.77)	4.18 (2.12–6.05)	3.44 (2.20–5.32)	0.35
TC, mmol/L	4.67 (3.80–5.61)	4.63 (3.57–5.68)	4.56 (3.79–5.41)	0.92
TG, mmol/L	1.30 (0.97–1.93)	1.59 (1.16–2.25)	1.61 (1.28–2.40)	0.006
HDL-C, mmol/L	1.11 (0.91–1.34)	1.07 (0.92–1.27)	1.02 (0.85–1.24)	0.17
LDL-C, mmol/L	3.12 (2.38–3.72)	3.06 (2.19–3.88)	2.94 (2.25–3.90)	0.99
BCAA, mmol/L	1.86 (1.30–2.09)	2.51 (2.40–2.67)	3.34 (3.08–3.95)	< 0.001
BCKA, umol/L	128 (106–155)	129 (116–137)	127 (119–131)	0.49

Data are presented as median (IQR) for continuous variables and number (proportion) for category variables. Differences in medians were examined using Kruskal–Wallis test among three groups; Differences in proportions were tested using the Chi-square test

BMI Body mass index, *WC* waist circumference, *FPG* fasting plasma glucose, *TC* total cholesterol, *HTN* hypertension, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FCP* fasting C-peptide, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *VFA* visceral fat area, *SFA* subcutaneous fat area, BCAA branched-chain amino acids, BCKA branched-chain keto acids

for Windows, Version 26.0. Armonk, NY: IBM Corp.); two - sided p-values < 0.05 were considered statistically significant.

Results

Clinical characteristics of the participants

As shown in Table 1, there were differences in the proportion of male and levels of triglyceride (TG), BMI and waist circumstance among groups divided by BCAA tertiles. No statistical differences were observed among three groups in duration of diabetes, blood pressure (systolic and diastolic), fasting C-peptide, fasting plasma glucose, glycosylated hemoglobin, fasting insulin, insulin resistance index, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and proportion of current smokers, current alcohol drinkers. However, there were no difference in levels of BMI and waist circumstance according to BCKA tertiles.

Obesity indexes according to various levels of BCAA or BCKA

As shown in Fig. 1, there were significant differences in the means of VFA among the three groups divided by BCAA tertiles ($p = 0.001$). The mean (cm^2) of VFA in the lower tertile group was significantly smaller than that in the middle tertile and upper tertile groups (94.7 versus 112.2, 94.7 versus 117.1, all $p < 0.05$). In ascending order, the means of SFA (cm^2) were 183.0, 204.8 and 206.4 among above three groups (p for trend = 0.02). Similar trends were also observed in the levels of BMI and WC according to the BCAA tertiles (all $p < 0.01$). However, the differences in VFA SFA BMI and WC were nonsignificant among groups classified by BCKA tertiles.

Association of BCAA with VFA

As shown in Fig. 2, Pearson correlation analysis indicated that BCAA was associated with common obesity parameters including BMI ($r = 0.234$, $p < 0.001$) and WC ($r = 0.242$, $p < 0.001$). Further analysis showed that BCAA was more closely associated with VFA ($r = 0.167$, $p = 0.005$) in comparison to SFA ($r = 0.136$, $p = 0.022$). However, BCKA was just correlated with SFA ($r = 0.122$, $p = 0.039$).

As shown Table 2, univariable linear regression analysis indicated BCAA was positively associated with BMI, WC, VFA and SFA (all $p < 0.05$), whereas, BCKA was only correlated with SFA ($\beta = 0.224$, $p = 0.039$). The association of BCAA and BMI, WC and VFA remained significant after adjusted for age and gender (Model 2) and further adjusted for duration of diabetes, systolic blood pressure, HbA1c, TG, HDL-C, smoking status, drinking status,

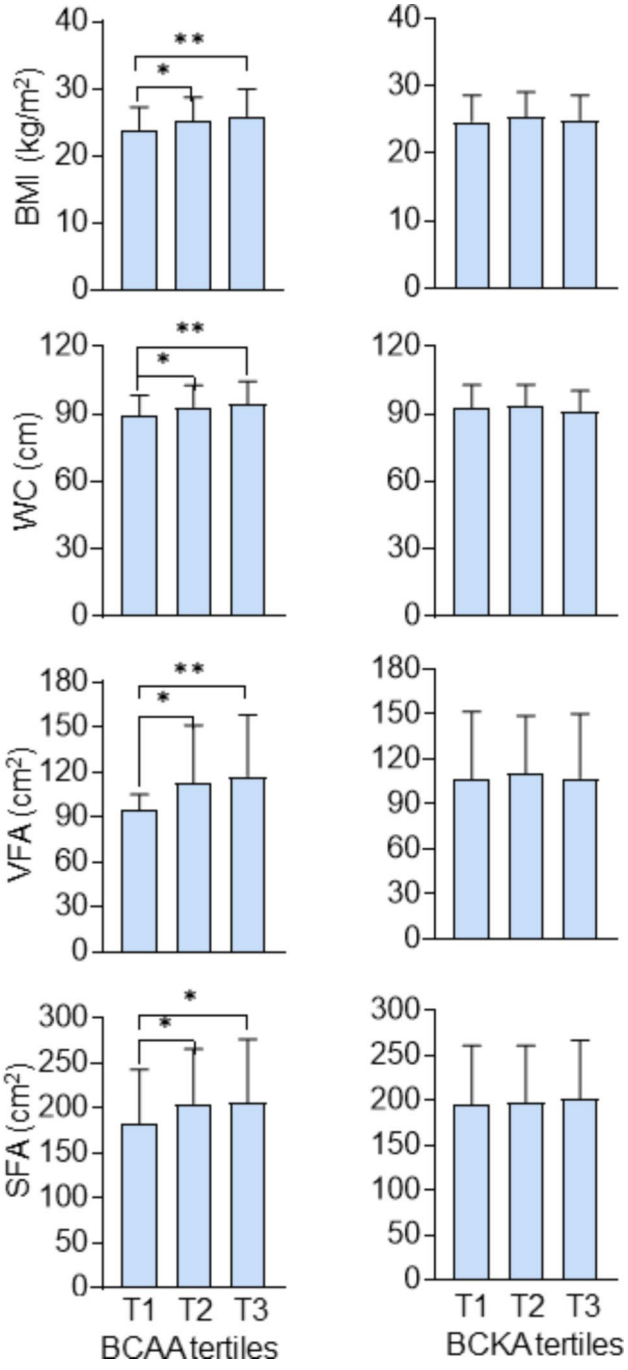

Fig. 1 Levels of obesity parameters according to tertiles of BCAA and BCKA. *$p < 0.05$, **$p < 0.001$. BMI Body mass index, WC waist circumference, VFA visceral fat area, SFA subcutaneous fat area, BCAA branched-chain amino acid, BCKA branched-chain keto acid

and Homeostasis model assessment for insulin resistance (HOMA-IR) (Model 3) (all $p<0.05$). Nevertheless, the correlation of BCAA and SFA became non-significant after adjustment for other confounders (Model 2, Model 3 in Table 2). Furthermore, the correlation of BCKA with obesity indices was of no statistical significance in multivariable regression analysis.

Discussion

Several interesting conclusions could be drawn in this study: (1) levels of serum BCAA were positively correlated with obesity parameters including BMI, WC, VFA and SFA; (2) BCAA was associated with VFA rather than SFA after adjustment for other confounders; (3) No correlation was observed between levels of serum BCKA and obesity indices considering other confounders.

Previous studies have pointed out BCAA was closely associated with obesity. A majority of studies demonstrated that elevated levels of BCAA in diet and serum were correlated with BMI and WC [8, 17, 20–22]. In animal studies, BCAA supplementation in diet increased perirenal white fat mass [23], whereas restriction of BCAA intake could rapidly reduce the abdominal fat mass [9, 24]. Our previous study also found that elevated BCAA intake deteriorated pancreatic steatosis in high fat diet (HFD) - fed mice [25]. In this study, our data also showed that serum BCAA was positively with BMI and WC as previously reported. However, there were few studies concerning the relationship between BCAA and VFA in patients with type 2 diabetes, although researchers pointed out that BCAA was associated with VFA in adolescents [14]. On the other hand, elevated VFA was associated with increased risk of diabetes and its complications including diabetic macro- and micro-vascular complications [26–29]. In this study, our data also demonstrated that BCAA was independently linked to VFA rather than SFA, indicating that reducing serum levels of BCAA (such as by restriction of its intake or accelerate BCAA catabolism) might reduce visceral fat accumulation, and further prevent patients from diabetic complications.

The mechanisms mediating BCAA and VFA are complicated. Firstly, acetyl-CoA from BCAA catabolism was an important source of de novo lipogenesis, and about 30% acetyl-CoA came from BCAA catabolism in adipogenesis [30]. Secondly, BCAA catabolism could promote adipocytes differentiation by amplifying the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in a Sirtuin 4 (SIRT4) dependent pattern [31]. Thirdly, BCAA was closely associated with insulin resistance. Research pointed out that BCAA supplementation could activated mammalian target of rapamycin complex 1 (mTORC1) and subsequent ribosomal protein S6 kinase, thus resulting in decreased insulin-induced phosphoinositide 3-kinase activity and subsequently impaired insulin signaling [32], on the other hand, insulin resistance could further accelerate lipogenesis [33]. Finally, visceral adipocytes might modulate levels of serum BCAA. Tan et al. point out that the levels of serum BCAA was dependent on the reduction of VFA after bariatric surgery [34].

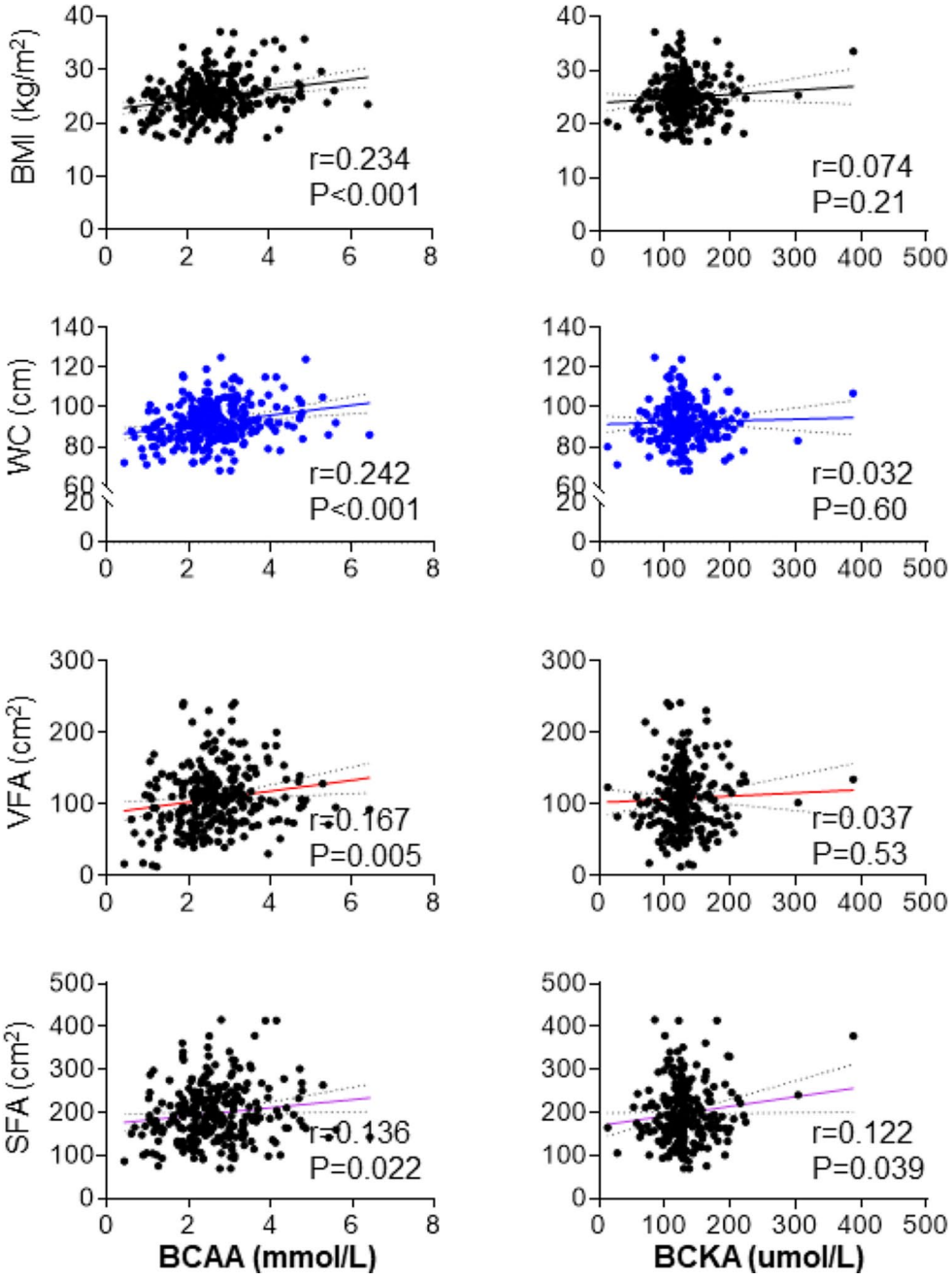

Fig. 2 Association of BCAA and BCKA with obesity parameters

Table 2 Correlation of BCAA and BCKA with each obesity parameter

	Model 1		Model 2		Model 3	
	β	*P* value	β	*P* value	β	*P* value
BMI						
BCAA	0.953	< 0.001	0.794	0.001	0.682	0.009
BCKA	0.008	0.214	0.007	0.284	-0.002	0.813
WC						
BCAA	2.553	< 0.001	1.988	0.002	1.643	0.018
BCKA	0.009	0.604	0.006	0.712	-0.016	0.378
VFA						
BCAA	7.670	0.005	6.649	0.016	6.120	0.039
BCKA	0.045	0.531	0.043	0.545	-0.012	0.881
SFA						
BCAA	9.502	0.022	7.563	0.068	5.741	0.198
BCKA	0.224	0.039	0.203	0.055	0.102	0.399

Data were analyzed using multiple linear regression analysis

In Model 1, independent variables included BCAA or BCKA; In Model 2, independent variables included age, gender and BCAA (or BCKA); In Model 3, independent variables included variables in Model 2 plus duration of diabetes, systolic blood pressure, HbA1c, TG, HDL-C, smoking status, drinking status, and HOMA-IR

BMI Body mass index, *WC* waist circumference, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *VFA* visceral fat area, *SFA* subcutaneous fat area, *BCAA* branched-chain amino acids, *BCKA* branched-chain keto acids

However, there were some limitations in our study. First, this was a cross-sectional study and more prospective studies should be warranted to explored their causal relationship between BCAA and VFA. Also, the mechanisms mediating the association between BCAA and VFA had not been investigated in this study. Moreover, the study subjects were restricted to patients with type 2 diabetes, and a majority of subjects were male, and the extrapolation of the conclusion to the whole population demands more large-scale studies.

Conclusions

In conclusion, levels of serum BCAA were more closely correlated with VFA than SFA, reduced levels of serum BCAA may help prevent visceral fat deposition and further diabetic complications.

Abbreviations

BMI	Body mass index
WC	waist circumference
FPG	fasting plasma glucose
TC	total cholesterol
HTN	hypertension
TG	triglyceride
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
FCP	fasting C-peptide
SBP	systolic blood pressure
DBP	diastolic blood pressure
VFA	visceral fat area
SFA	subcutaneous fat area
BCAA	branched-chain amino acids
BCKA	branched-chain keto acids

Supplementary Information

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Supplementary Material 1

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Author contributions

X C, W L and J L performed the statistical analysis and wrote the manuscript, J G, Y S and H W contributed to data collection, L Wand T L participated in the design of this study and reviewed the manuscript.

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Data availability

The datasets used and/or analyzed during the current study were available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Shanghai Putuo District Central Hospital (Shanghai University of Traditional Chinese Medicine Affiliated Putuo Hospital) has approved the research in accordance with the Declaration of Helsinki, with approval number: PTEC-A-2024-40(S)-1. Informed consents were acquired from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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